

REMARKS

Prior to this Amendment, Claims 1-22 were pending and under consideration. With this Amendment, Claim 1 is being amended and Claims 23-25 are being added. No claims have been canceled. Thus, after entry of this Amendment, Claims 1-25 are pending and under consideration. The amendment of Claim 1, the addition of Claims 23-25, and the outstanding objections and rejections are addressed in detail, below.

Amendments of Claim 1:

Claim 1 is amended to correct minor grammatical inaccuracy. The amendments do not introduce any new matter.

Addition of Claims 23-25:

Claims 23-25 are added to recite an embodiment in which the microbubbles have an outer shell consisting of a single layer of a biodegradable polymer. Support for Claims 23-25 can be found, for example in the Specification at page 7, lines 1-35, where microbubbles having a single layer outer shell and method of making them are described. Accordingly, no new matter is presented by new Claims 23-25.

Rejections under 35 U.S.C. § 102(e)

Claims 1-22 stand rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by U.S. Patent No. 5,944,666 to Hossack *et al.* ("Hossack *et al.*"). According to the Examiner, Hossack *et al.* teach a method of delivering contrast agents into a blood vessel comprising the steps recited in instant Claim 1. Applicants traverse the rejection.

As the Examiner knows, a claim is anticipated under 35 U.S.C. § 102 only if each and every limitation as set forth in the claim is found, either expressly or inherently, in a single prior art reference. Hossack *et al.* do not teach each and every limitation recited in instant Claim 1.

Claim 1 recites a method of site-specific delivery of a therapeutic agent or a diagnostic agent comprising introducing an agent-loaded microbubble population into a region of interest in which the microbubble population has a *controlled fragility*. The controlled fragility is characterized by a wall thickness to diameter ratio that defines a threshold power intensity value

of ultrasound energy where microbubble rupture occurs in the population. An ultrasound signal is applied to the region of interest at a power intensity sufficient to induce microbubble rupture. The power intensity is maintained until at least a substantial number of microbubbles are ruptured.

Hossack *et al.* teach a method of assessing flow characteristics in a vessel. In Hossack *et al.*, a set of ultrasound signals having a first power intensity are transmitted into a first region of the vessel to selectively rupture a contrast agent in the first region, thereby creating a volume of blood in the vessel having a reduced concentration of the contrast agent. Then, a set of ultrasound signals having a second power intensity are transmitted into a second region of the vessel, which is positioned downstream of the first region, to image the contrast agent in the second region. The second power intensity is lower than the first power intensity. As taught by Hossack *et al.* in Claim 1, *the ultrasound signals with lower power intensity rupture the contrast agent to a lesser extent than the ultrasound signals with higher power intensity.* In other words, the microbubbles taught by Hossack *et al.* do not have a *controlled fragility*, i.e., a microbubble population having the characteristics of being rupturable when exposed to acoustic energy equal to or greater than a predetermined intensity or threshold. Below this threshold, substantially all the microbubbles remain intact, while above the acoustic intensity threshold the microbubbles rupture. Please refer to the description in the Specification at page 3, lines 11-16.

Accordingly, for the reasons stated above, Applicants submit that independent Claim 1, and hence all claims that depend therefrom (Claims 2-22), are not anticipated by Hossack *et al.* Applicants therefore respectfully request the rejection of Claims 1-22 over Hossack *et al.* be withdrawn.

Regarding Claims 5-8, the Examiner argued that “ultrasonic microbubbles inherently comprise an outer layer of biologically compatible amphiphilic material and an inner layer of a biodegradable polymer comprising the claimed various polymer selections.” Applicants disagree.

In relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristics necessarily flows from the teaching of the applied prior art. *Ex parte Levy*, 17

USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. *In re Robertson*, 169 F.2d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Applicants respectfully submit the Examiner has not met the burden of showing that the bi-layer structure of the microbubbles recited in instant Claims 5-8 is an inherent characteristic that necessarily flows from the teaching of Hossack *et al.*

Claims 5-8 recite microbubbles that have *an outer layer* of biologically compatible amphiphilic material and *an inner layer* of a biodegradable polymer. The microbubbles taught by Hossack *et al.* do not have bi-layered shells. In fact, not all microbubbles have bi-layered shells and some microbubbles may have single layer shells. For example, U.S. Patent No. 6,071,495 (“Unger *et al.*”), cited by the Examiner in this Office Action, teach gas-filled liposomes that have either a *multilamellar* membrane shown in FIG. 9 or a *unilamellar* membrane shown in FIG. 10. There is no reason to draw the conclusion that the microbubbles taught by Hossack *et al.* have bi-layered shells.

Applicants have reviewed U.S. Patent No. 6,071,495 to Unger *et al.* (“Unger *et al.*”), cited but not rely upon by the Examiner. Unger *et al.* teach lipid microspheres filled with a gas or gas precursor. However, Unger *et al.* do not teach or suggest microbubbles having a controlled fragility, as recited in the instant claims.

Conclusion

Based on the foregoing, Applicant submits that Claims 1-25 are in conditions for allowance. An early indication of the same is therefore respectfully requested. If any matters can be resolved by telephone, the Examiner is invited to call the undersigned attorney at the telephone number listed below. No fees beyond those being submitted concurrently herewith are believed due. However, the commissioner is authorized to charge any additional required fees, or credit any overpayment, to Dorsey & Whitney LLP Deposit Account No. 50-2319 (Order No. A-72273/AMP/TJH (470255-37)).

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Respectfully submitted,

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